Adenine phosphoribosyltransferase部分欠損による2,8-dihydroxy adenine結石

AUTHOR(S):

竹内, 秀雄; 友吉, 唯夫; 高橋, 陽一; 吉田, 修

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2, 8-DIHYDROXY ADENINE UROLITHIASIS ASSOCIATED WITH INCOMPLETE ADENINE PHOSPHORIBOSYLTRANSFERASE DEFICIENCY

Hideo TAKEUCHI*, Tadao TOMOYOSHI*, Yoichi TAKAHASHI,
Osamu YOSHIDA, Michihico UCHIDA and Toru NAKAMURA
From the Departments of Urology and Internal Medicine, Faculty of Medicine, Kyoto University, Kyoto, Japan

ABSTRACT

A case of 2,8-dihydroxy adenine stones with incomplete deficiency of adenine phosphoribosyltransferase is reported. Adenine phosphoribosyltransferase activities of the family members were normal. This case is believed not to be hereditary.

INTRODUCTION

Cases of 2,8-dihydroxy adenine stones are very rare; to date only three cases have been reported in the literature[1,2]. All three were homozygous for a deficiency of adenine phosphoribosyltransferase (APRTase). We report a case of 2,8-dihydroxy adenine stone formation with incomplete APRTase deficiency.

CASE REPORT

The propositus, a boy born in February, 1970, had passed small stones since the age of five months. He was referred to the urology clinic at the age of nine months. Urinalysis revealed microscopic hematuria, crystalluria and aciduria. The crystals were brown and round (Fig.1). An IVP showed a round filling defect in the right renal

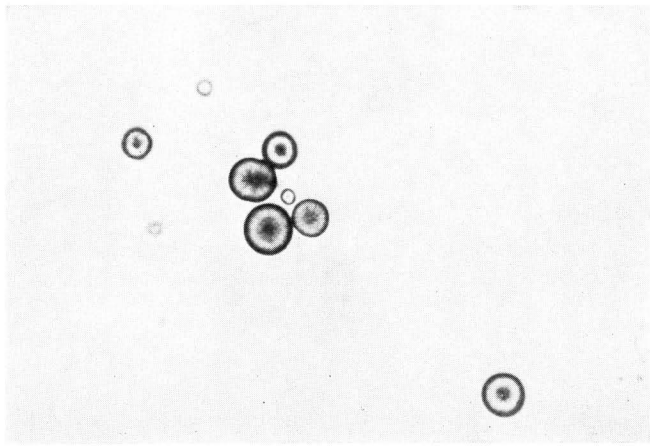

Fig. 1. Brown round crystals in the urine. ×400

* Present address: Department of Urology, Shiga University of Medical Science, Otsu, Shiga, Japan 520-21

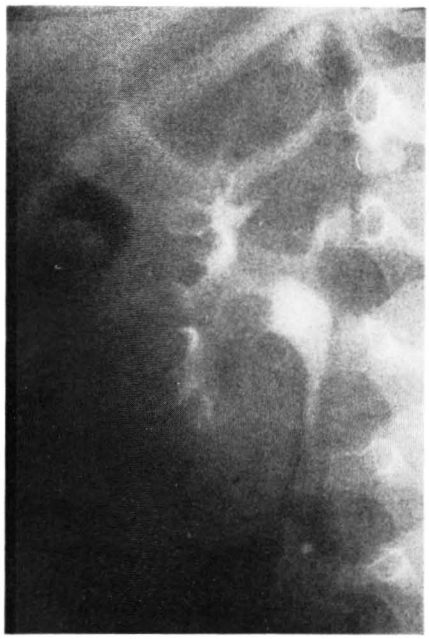

Fig. 2. IVP showing a round filling defect in the right renal pelvis.

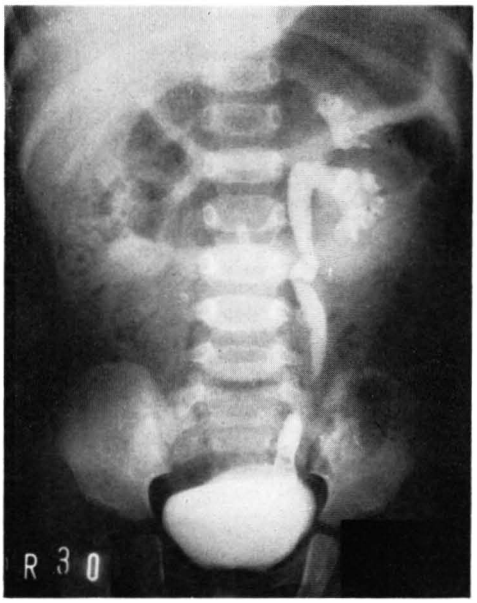

Fig. 3. IVP showing non-visualization of the right kidney and left hydronephrosis. In the lower portion of the left ureter three filling defects are seen.

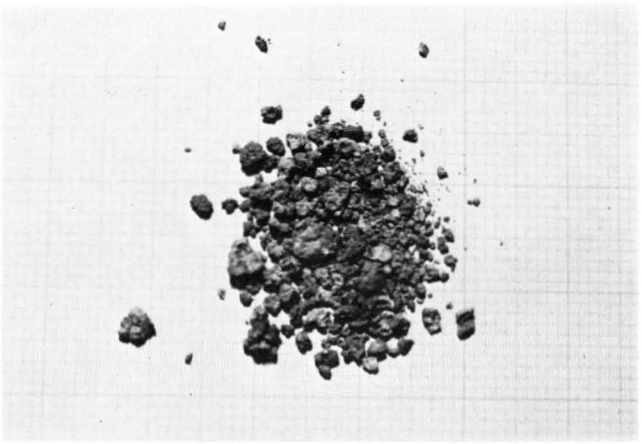

Fig. 4. The stones are brown and friable.

pelvis (Fig. 2). Uric acid urolithiasis was suspected, and the patient was treated with sodium bicarbonate (1.0 g/day). Urine acidity decreased to pH 6.5, but the patient passed several small stones. An IVP at the age of eighteen months showed non-visualization of the right kidney and left hydronephrosis due to ureteral stones (Fig.3). The patient was first admitted to our urology department in September, 1971. His growth was normal with height and weight within the expected range. Intelligence seemed normal, and self mutilation and choreic movements were never observed. The plasma uric acid level was 5.1 mg/dl and its urinary excretion was 12 mg/kg/24 hours. Uric acid clearance was 4.7 ml per minute. Other routine laboratory findings

were normal.

Left ureterolithotomy was done. The stones were brown and friable (Fig.4). Examination of the stones by infra-red spectrometry revealed a uric acid like compound.

After operation treatment with bicarbonate was continued. An IVP at the age of 20 months showed recovery of function of the right kidney, but it looked somewhat small. The patient occasionally passed small stones until 1974, but since then no stones have been passed and urinalysis has been normal.

Re-examination of the stones revealed them to be pure 2,8-dihydroxy adenine (Fig.5). Adenine metabolites in the urine were examined by chromatography and high voltage electrophoresis. The presence of adenine and 2,8-dihydroxy adenine was

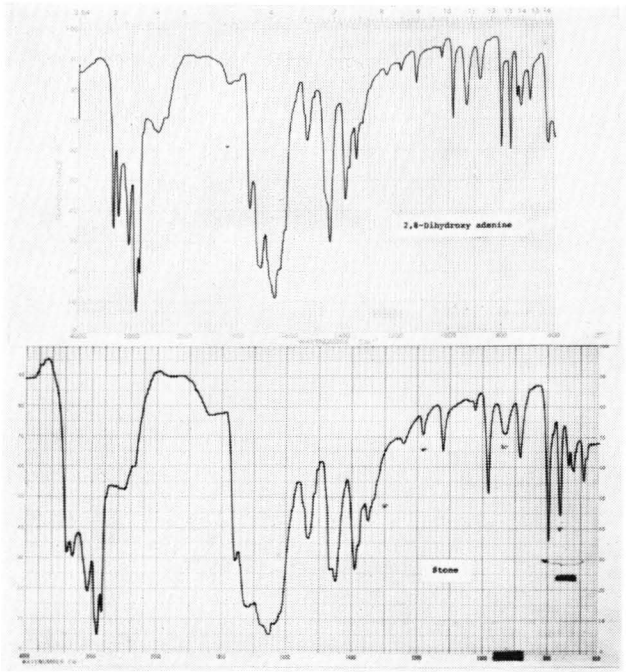

Fig. 5. Infrared spectrum of 2, 8-dihydroxy adenine (upper) and of the stone (lower), examined as nujol mulls.

Table 1. Hypoxanthine guanine phosphoribosyltransferase (HGPRTase) and adenine phosphoribosyltransferase (APRTase) activity in th family members.

	HGPRTase activity (n moles of synthesized IMP/mg protein/hr.)	APRTase activity (n moles of synthesized AMP/mg protein/hr.)
K.M. (propositus)	118.2	2.7
F.M. (father)	97.8	23.2
S.M. (mother)	103.0	17.9
M.M. (sister)	99.9	25.0
R.M. (sister)	99.9	25.0
Control (mean ± S.D.) n = 10	91.8 ± 13.9	22.7 ± 7.8

HGPRTase and APRTase activities were measured in erythrocyte lysates by a radioassay employing [8-^{14}C] hypoxanthine and [8-^{14}C] adenine, respectively, with separation of purine nucleotide reaction products from purine bases by thin layer chromatography.

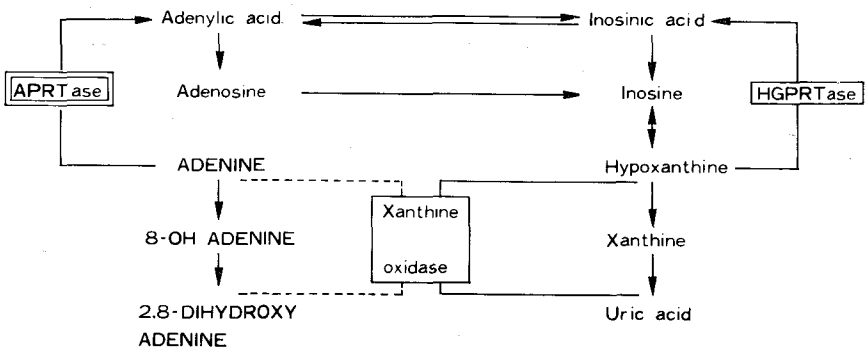

Fig. 6. Major pathways for the metabolism of adenine.

proved, suggesting a block in the adenine reutilization pathway. Enzyme activity was determined in erythrocyte lysates. Hypoxanthine guanine phosphoribosyltransferase (HGPRTase) activity was normal but adenine phosphoribosyltransferase (APRTase) was only about 10 percent of normal. These enzyme levels were normal in both parents and the two sisters of the patient (Table 1).

DISCUSSION

In the three cases of 2,8-dihydroxy adenine stone with complete deficiency of APRTase previously reported the condition appeared to be homozygous[1,2]. The present case is thought to be the first reported of 2,8 -dihydroxy adenine stone with incomplete deficiency of the enzyme.

2,8-dihydroxy adenine is normally undetectable in the urine[1], and the formation of 2,8-dihydroxy adenine stones is a direct consequence of the enzyme defect; in the absence of APRTase, adenine has only one available alternative pathway in man[3], oxidation by xanthine oxidase to 2,8-dihydroxy adenine[4] (Fig.6). 2,8-Dihydroxy adenine is much less soluble than uric acid and is nephrotoxic due to intratubular precipitation[5]. A combination of allopuriol therapy and a low purine diet inhibit somewhat the formation of 2,8-dihydroxy adenine[1].

The partial deficiency of APRTase may be a relatively common disorder, and it has no clear clinical features[6]. Erythrocytes from subjects with a partial deficiency show 20 to 50% normal APRTase activity[1,2,6,7]; APRTase activity in this patient was only 10% of the normal value. This enzyme deficiency presumably induced 2,8-dihydroxy adenine stone formation.

Recent studies suggest that the APRTase gene is on chromosome number 16[8] and that the male to female ratio is approximately equal[6], but the possibility of spontaneous mutation of APRTase is not always denied[6,9]. The fact that the APRTase activity in the family members was normal suggests the possibility of spontaneous mutation of APRTase. In order to ascertain that the enzyme deficiency in this case is a result of spontaneous mutation, a further investigation of APRTase activity in other tissues is necessary.

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和文抄録

Adenine phosphoribosyltransferase 部分欠損による 2, 8-dihydroxy adenine 結石

京都大学医学部泌尿器科学教室（主任：吉田　修教授）
竹内　秀雄*・友吉　唯夫*・高橋　陽一・吉田　修

京都大学医学部第1内科学教室（主任：内野治人教授）
内田三千彦・中村　徹

adenine phosphoribosyltransferase の部分欠損による 2,8-dihydroxy adenine 結石の1例を報告した．家族の APRT 活性測定では全員正常で遺伝関係認められず spontaneous mutation の可能性が示唆された．

* 現　滋賀医科大学医学部泌尿器科教室